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# Secular changes in human reproduction and assisted reproductive technologies

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Abstract: Since the middle to late 20th century the majority of children born in the developing world have been likely to enter into post-reproductive age. Currently, child mortality is at its lowest level in human history. While more children are living to post reproductive age, approximately 15% of couples are experiencing infecundity. This is either a result of one or both members of the couple being infecund, or, despite both being fecund, the interaction between them prevents fertility for some reason. Assisted reproductive technologies have provided many infertile couples an opportunity to have children. Assisted reproductive technologies operate by intervening and manipulating gametic and intrauterine natural selection. This paper discusses the possible influence of assisted reproductive technologies on child development. This paper outlines some of the reported changes in children resulting from assisted reproductive technologies. Although, few people are either aware or care about possible long term consequences of relaxed natural selection contributed by medical intervention (i.e. assisted reproductive technologies) we have little understanding to what extent such medical interference may affect long term fitness in humans.

Key words: The self-amplifying mechanism of human evolution

In 1969 Polish anthropologist Tadeusz Bielicki (1969) proposed that human evolution, unlike that of many other life forms, has been driven by autocatalytic (self-amplifying) rather than homeostatic mechanisms. In autocatalytic mechanisms, change in one biological characteristic of an evolving lineage, through a set of feedback loops enforces similar changes in other characteristics that demand further changes in other characteristics, including the initiating one. Thus, biological changes such as the appearance of cooperative parenting approximately 4.5 Ma ago (Clark and Henneberg 2015; 2017) may have resulted in the development of language that, in turn influenced food acquisition via collaborative

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hunting and improvement in the production and use of weapons and tools that led to the management of the human environment (Olney et al. 2015) that eventually improved cooperative parenting. The majority of biological processes in organisms and between organisms and their environment are of homeostatic nature: when the level of a particular enzyme in a body increases, physiological mechanisms react by stabilising or lowering this level. When a population of a particular species increases so much that it strains resources of the environment, the lack of resources results in decrease of the population. A balance between an organism, or a population and its environment is maintained. Not in humans.

Human manipulation of the environment provided a non-genetic way of evolutionarily important information transmission that allowed faster than inter- generational evolutionary change (Strzalko and Henneberg 1982). Ability to consciously manipulate the external world, combined with linguistic abilities of symbolic representations produced a unique in the animal world human ability to decorate and modify their own bodies. These characteristics of human evolution – self amplification, non-genetic transmission of information and control of the environment, including human bodies – are still operating today influencing complex social systems. Results of their amplification are ultimately limited by the capacity of patients' organisms. Self-amplifying relations tend to increase their rate of change and growth. Thus, if unchecked may produce runaway expansion. Such runaway expansions happen in simple chemical self-amplifying systems. Most explosives work this way. Self-amplification also includes nuclear chain reactions with their daunting consequences (Hanopolskyi et al. 2021). As these last two examples indicate, positive feedback systems, if unchecked, terminate only when the entire system reaches singularity and collapses. However, self-amplifying systems have been recently used successfully to produce RNA-based anti-SARS-CoV-2 vaccines (Bloom et al. 2021) indicating their usefulness when appropriately controlled.

There is an obvious need to produce a transition of the human system into a homeostatic one. Most homeostatic systems involve negative feedbacks, instead of positive ones, where increase or expansion of one of its parts results in the decrease or regression of some other parts. Whether such change to a homeostatic system is possible without incurring catastrophic consequences is an open question. The ecological capacity for humans existing on the Earth is obviously limited while settlement of other planets is yet impossible due, not just to technological limitations of the survival in space, but also the population genetics requirements of maintaining independent self-reproducing human populations in isolated settlements – the population size required to avoid effects of inbreeding and genetic drift is too large to be supported independently by currently available technologies (Saniotis et al, 2020). The obvious logical consequence of this consideration is to limit the natural growth of the Earth's human population to achieve its stable size. Since, however, human reproductive activities are complex and dynamic, their perfect stabilisation seems impossible. Significant decrease in natural growth of human global population, through the feedbacks between population size and its age structure and economy is as dangerous to our survival as positive growth (Peterson 2017). Limiting just one element of the human system is not a solution. The entire system needs to be changed.

The advent of antibiotics in the half of the 20$^{th}$ century further decreased child mortality and premature death from infections (Saniotis and Henneberg 2011). It needs to be remembered that throughout human history the Biological State Index (Henneberg and Piontek 1975, Henneberg 1976) values wavered around 0.20–0.30 (Saniotis and Henneberg 2011). The Index measures an opportunity of an average individual to pass their genes to the next generation. Before the Second Epidemiological Transition (mid 19$^{th}$ century) natural selection due to differential mortality permitted ~50% of neonates to survive to mid adolescence (15 years of age) with some surviving individuals being further removed during their reproductive lives (Saniotis and Henneberg 2013; Saniotis and Henneberg 2011; Budnik et al, 2004; Stephan and Henneberg 2001).

It was only since the middle to late 20$^{th}$ century that the majority of children born in the developing world have been likely to enter into post-reproductive age (Saniotis and Henneberg 2011). Currently, child mortality is at its lowest level in human history. Since 1990 to 2017 child mortality has showed a >50% reduction (from 12.6 million to 5.4 million) (Roser et al. 2013). In the late 20$^{th}$ century and early 21$^{st}$ century biological systems, be it whole organisms, or their parts and component chemicals became manipulated by technological means to prevent or control several types of congenital disorders such as phenylketonuria, enabling neonates to develop into adults and enter into reproductive life. However, while modern biotechnology has been able to reduce results of several types of fitness reducing alleles, it has been argued that such alleles may have had an adaptive role in the past (Agrawal and Whitlock 2012, Keightley and Otto 2006). Consequently, Saniotis et al. (2020) have pointed out that medical intervention has contributed to an excess burden of fitness reducing alleles in the human gene pool, or what is referred to as genetic load.

Genetic load tends to have an accumulative effect, in relation to both congenital and infectious diseases. Medical intervention not only enables more deleterious genes to increase in the human population but also exerts a selective pressure resulting in disease/pathogen evolution with subsequent fitness loss in humans while pathogens increase in virulence (Stephan and Henneberg 2001; Ewald 1994). The global rise of anti-biotic resistant bacterial strains exemplifies this selective phenomenon.

Saying this, few people are either aware or care about the long term consequences of genetic load as long as medicine is available. However, this means that our dependence on medical intervention will continue to increase, with possible reduction to our long term fitness.

## Current secular trends in human reproduction and assisted reproductive technologies

Currently, infecundity rates in couples are approximately 15% worldwide (Karabulut et al. 2018; Gerrits et al. 2017). Fecundity is the ability to produce offspring, thus infecundity is the condition of a parental organism that precludes production of offspring. Fertility is actual production of offspring, that necesessarily involves two parents and thus infertility may be a result of individual infecundity, of incompatibility of fecund parents or of their choice to have no offspring. In some populations infertility has reached 30% (Ombelet et al. 2008; Nachtigall 2006; Inhorn and Patrizio 2015). Both sexes can have their fecundity affected. However, there are conflicting reports on the rate of infertility patterns worldwide. Mascarenhase et al (2012) found that apart from Sub-Saharan regions, there was little evidence in global infertility changes since 1990. In contrast, Sun et al's (2019) study on the burden of infertility in 195 countries and territories, revealed that the 35–39 years age group had the highest infertility prevalence rate while the 15–19 years age group (both sexes) had the lowest infertility prevalence rate (both sexes) (Sun et al. 2019). This lack of concensus on global infertility rates should not overlook the fact that many couples worldwide are currently using Assisted Reproductive Technologies as they cannot have children in the normal manner.

While many studies have focused on female infecundity prevalence, male infecundity prevalence matches female rates in several countries. For example, in 30–50% of couples infertility is due to male causes (Tournaye and Cohlen 2012).

There are several risk factors which are contributing to current secular infertility trends in men and women. These include genetic causes, aging, infectious diseases, lifestyle factors such as increased sedentism and overweight/obe-

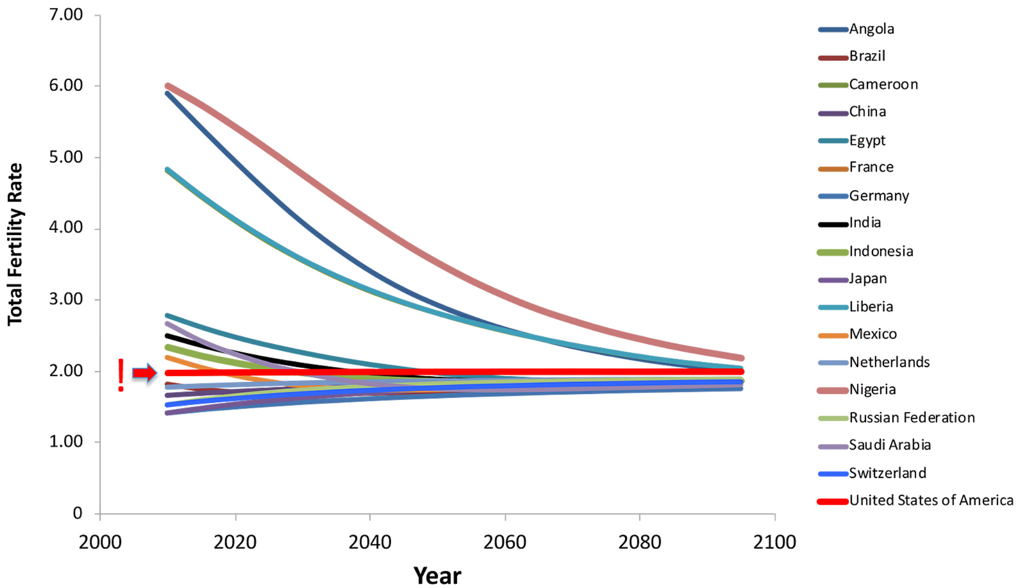


Fig. 1. United Nations Population Council fertility predictions (https://population.un.org/wpp/Download/Probabilistic/Fertility/). Total Fertility Rate is a number of children born to an average female during her lifetime. Note reducing variability through time. The red arrow with an exclamation mark indicates the rate close to two children per woman – a minimum required to maintain population size since two children are needed to replace the mother and the father in the next generation provided there is no premature mortality

sity, smoking, delayed procreation and environmental pollution (Schmidt et al. 2012; Cong et al. 2016; Esmaeilzadeh et al. 2016; Thoma et al. 2021; D'Angelo and Meccariello 2021). For example, one study identified that infertile women were 3.8 fold more likely to be overweight and 4.8 of being obese (Esmaeilzadeh et al. 2016).

From an evolutionary viewpoint, many of the prevailing problems associated with fertility decline may be due to an evolutionary "mismatch" between how ancestral humans lived and the novel lifestyles which humans currently engage in. Indeed, the latter have been blamed for disrupting homeostatic mechanisms (Eaton et al. 1998; Eaton et al. 2002).

Increasing infertility has popularised assisted reproductive technologies. Assisted reproductive technologies have provided many infertile couples an opportunity to have children. Assisted reproductive technologies incorporate a series of medical techniques used to achieve pregnancy. Over the last forty years several reproductive assisted technologies have been developed. These include in-vitro fertilization (IVF), embryo transfer, intracytoplasmic sperm injection (ICSI) and surrogacy (Farquhar and Marjoribanks 2018 Novakovic et al. 2019). Since 1978, assisted reproductive technologies have resulted in more than 7 million births (Adamson et al 2018).

Assisted reproductive technologies operate by intervening and manipulating gametic and intrauterine natural selection. For instance, during IVF, spermatozoa are artificially selected irrespective of their natural fitness status. It has been argued that such artificially selected spermatozoa would probably under normal reproductive conditions be unable to induce fertilization (Hanevik et al. 2016). Epidemiological studies on assisted reproductive technologies also note an infrequent likelihood in imprinting disorders relating to epigenetic interference during early development (Lazaraviciute et al. 2014; Gosden et al, 2003; Le Bouc et al. 2010; Kohan-Ghadr et al. 2016 ).

Similarly, IVF artificially alters selection processes on subjected oocytes via inducing controlled ovarian stimulation. Second, cryopreservation techniques are often used for transferring embryos, hence, creating a novel selection process. Cryopreservation allows for less than favourable embryos to be selected (Mastenbroek et al, 2011).

Third, socioeconomic factors also inform selection process connected to assisted reproductive technologies. Availability of IVF is expensive and biased against low income health sub-fertile couples. Also, IVF is mainly available in developed countries with lower availability in low-income nations (Ombelet et al. 2008). Consequently, IVF tends to favour healthy sub-fertile couples from richer countries (Ombelet et al. 2008; Hanevik et a. 2016). Additionally, companies offering IVF have various selective criteria which can discriminate against individuals/couples from accessing this technique. These include obesity, smoking, hepatitis infection or immunodeficiency status (Hanevik et al. 2016). In other words, current medical fertility practices are creating new kinds of selection processes, which may increase dependency on reproductive assisted technologies by many sub-fertile couples in the future.

Several studies have noted likely epigenetic changes due to assisted reproductive technologies, such as, substantial differences in methylation in C9orf3, H19/IGFsand TNP1 areas (Castillo-Fernandez et al. 2017); hypermethylation (Melamed et al. 2015); significant methylation difference in SNORD114-9 CpG between intracytoplasmic sperm injection (ICSI) and control groups (El Hajj et al, 2017), and significantly lower DNA methylation in children produced by ICSI than children in the control group at the time of birth (Estill et al. 2016).

Also, alterations in DNA, chromatin structure and miRNA expression to shifts in trophoblast infiltration and transfer were identified (Mani et al. 2020; Maccani and Marsit 2011; Kohan-Ghadr et al. 2016). This finding denotes the critical role of epigenetic regulation in correct placentation, and inconsistency from this regulation by assisted reproductive technologies could have unfavourable consequences (Nelissen et al. 2011; Mani et al. 2020).

Other reported epigenetic changes in children produced by in-vitro fertilisation are deficits in systemic and pulmonary vascularity (Scherrer et al. 2012), alterations in body composition and cardiometabolic processes (Ceelen et al. 2007, 2008), and improved growth and metabolism (Miles et al. 2007). Long term evaluation is needed regarding whether such epigenetic changes in offspring produced by assisted reproductive technologies have long term health effects (Hanevik et al. 2016). Additionally, several meta-analyses have reported increased risk of placenta previa, preeclampsia, low birth weight (< 2500g) and intrauterine growth constraints in singleton IVF pregnancies (Pandey et al. 2012; Mani et al 2020; Zhu et al. 2016; Kalra et al. 2011). Use of assisted reproductive processes is clearly more expensive than natural fertility. Consequences of the processes will further add medical costs to the maintenance of human life. As long as it is economically feasible there should not be an objection to their use, however, it should be kept in mind that they increase human vulnerability, especially in crisis situations.

## Conclusion

Modern humans are not exempt from evolutionary processes, as indicated in several studies which show increasing prevalence of heritable traits as a consequence of relaxed natural selection, such as spina bifida occulta, tarsal coalition, median artery of the forearm, as well as the recent disappearance of the thyroidea ima artery (Saniotis and Henneberg 2020; Hanevik et al. 2016; Solomon et al. 2009; Lee et al. 2010; Bhatia et al. 2005). Additionally, based on the Framingham Heart Study, Stearns et al. (2010) have predicted that natural selection is altering systolic pressure and age at first reproduction. Since fertility is a major factor in informing human populations, the influence of fertility on selection is significant to childless couples who have the option to use assisted reproductive technologies (Hanevik et al. 2016). However, as Saniotis et al. (2020) point out possible genetic load may facilitate unfavourable and fitness constraining alleles in the human population. Certainly, heritable traits in women such as polycystic ovaries and endometriosis and hypospadias in men are fitness reducing since they have a direct impact on human fertility (Hanevik et al. 2016). Although, it is too early to measure fertility trends of individuals who were a result of IVF, Hanevik et al. (2016) suspect that IVF individuals will have higher subfertility rates. In any case, increasing infertility and availability of assisted reproductive technologies exemplifies medicine's impact in influencing current and future human fertility.

## The Authors' contribution

Both AS and MH developed the thematic structure and analysis of the paper, and were involved in every draft, as well as editing and proof reading.

## Conflict of interest statement

The authors declare that there is no conflict of interest.

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